REMARKS

Claims 1-3 are pending and await further action on the merits.

Issues under 35 U.S.C. 102(b)

The Examiner has maintained the rejection of claims 1-3 under 35 U.S.C. 102(b) as being anticipated by Kaspersen et al. (Journal of Label. Comp. and Radiopharm., Vol. 27, No. 9, 1055, 1989). Applicants respectfully traverse the rejection.

The Examiner takes great effort in the outstanding Office Action to point out that Applicants' burden is to replicate the experiments of Kaspersen et al. to prove that the drying conditions of Kaspersen et al. would not necessarily provide mirtazapine crystals having (i) a water content of not more than 0.5% by weight and (ii) a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours, as presently claimed.

Applicants understand the Examiner's arguments; however, Applicants firmly believe that the disclosure of Kaspersen et al. is not sufficiently close to the presently claimed invention such that the burden has been shifted to Applicants to replicate the experiments of Kaspersen et al. Applicants now discuss the distinctions between Kaspersen et al. and the present invention.

1) Novelty

The crystals disclosed by Kaspersen et al. are those of a "^{13}C-compound". Therefore, crystals of unlabeled mirtazapine of the present invention are quite different from those disclosed by Kaspersen et al.

As is apparent from the whole disclosure of the present specification, the compound of the present invention is an unlabeled compound, which is useful as an antidepressant for therapeutic applications to human bodies. It would be clear to the artisan that the compound of the present invention contains an isotope in a naturally occurring ratio. To the contrary,

Kaspersen et al. disclose a ^{13}C-labeled compound for metabolic studies in the column of "INTRODUCTION".

There are certain teachings in Kaspersen et al. which show that the unlabeled compound is clearly distinguished from the labeled compound by Kaspersen et al. First, Kaspersen et al. denote an unlabeled compound as "Org 3770", and a ^{13}C-labeled compound as "^{13}C-labeled material" (see column of "SUMMARY" of Kaspersen et al.) or "^{13}C-Org 3770" (see page 1057 of Kaspersen et al.). Second, the compound 1c has a melting point of 123.8-125.8°C. On the other hand, the low-hygroscopic mirtazapinc crystals of the present invention have a melting point of 114-116°C as is clear from Example 7 of the present specification. Therefore, these compounds are distinct from each other.

Accordingly, Applicants respectfully submit that it makes no sense to follow the Examiner's suggestion and repeat the drying process of Kaspersen et al., since the drying process of Kaspersen et al. would provide a dried labeled composition. Such a dried labeled composition is irrelevant to the claimed invention having an isotope in a naturally occurring ratio.

2) Unobviousness

The present specification discloses in Example 8 that a crude mirtazapine is recrystallized from methanol/water and dried under reduced pressure (4 to 5.3 kPa) at 50° to 60°C, to give crystals having a water content of not more than 3.5 % by weight, and that the crystals are hemihydrate as is clear from the results of X-ray diffraction.

The present specification also discloses in Example 7 that low-hygroscopic anhydrous mirtazapinc crystals having a water-content of 0.1% are obtained by drying the hemihydrates obtained in Example 6 under reduced pressure of 1330 to 1862 Pa at 90° to 95°C.

However, Kaspersen et al. do not disclose or suggest that hemihydrate mirtazapine is heated to dry at a temperature higher than ordinary heating temperatures. Therefore, the low-hygroscopic anhydrous mirtazapine crystals of the present invention cannot be expected from Kaspersen et al.

The document, "Extract from Hunnius Pharmazeutisches Wörterbuch, 8th Edition, de Gruyter 1998, page 682, which has already been filed with the U.S.P.T.O. in the November 23, 2004 IDS, discloses as follows:

> "Water of hydration: Water as a structural element of the crystal lattice of a substance; due to the strong fixation removal of the water of hydration is only possible by higher temperatures with destruction of crystal." (Emphasis added).

Therefore, it cannot be expected that anhydrous crystals are obtained by heating the hydrate or hemihydrate of crystals at high temperatures, because a person skilled in the art would usually avoid heating the crystals at high temperatures.

As is explained above, even if the compound 1c disclosed by Kaspersen et al. is low-hygroscopic anhydrous mirtazapine, the compound 1c is not an unlabeled compound but a ^{13}C-labeled compound. Actually, the compound 1c has a melting point of 123.8-125.8°C. On the other hand, the low-hygroscopic mirtazapinc crystals of the present invention have a melting point of 114-116°C as is clear from Example 7 of the present specification. Therefore, these compounds are distinctly distinguished from each other.

Kaspersen et al. do not disclose or suggest that the crystals obtained from a methanol/water solvent are crystals of a hydrate. However, even if the crystals of the label compound disclosed by Kaspersen et al. are hydrate, the crystals of the mirtazapine hydrate of the present invention cannot be expected from Kaspersen et al., because the mirtazapine hydrate of the present invention is not a labeled compound as disclosed by Kaspersen et al. but an unlabeled compound.

Accordingly, the crystals of the present invention are different from the crystals disclosed by Kaspersen et al., and cannot be expected from Kaspersen et al. As such, withdrawal of the rejection is respectfully requested.

With the above remarks, Applicants believe that the claims, as they now stand, define patentable subject matter such that passage of the instant invention to allowance is warranted. A Notice to that effect is earnestly solicited.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Garth M. Dahlen, Ph.D., Esq. (Reg. No. 43,575) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

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Respectfully submitted,

By Gat M Dal #43575 for

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